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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,453	07/18/2006	Matthew David Osborne	BJS-620-412	4519

23117 7590 04/06/2011

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/06/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,453	OSBORNE ET AL.	
	Examiner	Art Unit	
	MARIA MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9,10,13-16,33,36,41 and 45-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,9,10,13-16,33,36,41 and 45-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to an amendment filed 2/7/11. Claims 1, 4, 9, 10, 13-16, 33, 36, 41 and 45-50 are pending in this application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 9, 10, 13-16, 33, 36, 41 and 45-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Field et al (US 6,593,140; see entire document) in view of Gorfien et al (US 20060148074; see entire document). **This rejection is maintained for reasons below.**

Applicants claim a method of culturing myeloma cells in media lacking transferring, lacking lipophilic chelators and lacking synthetic and/or lipophilic nitrogen containing chelators and in the presence of ferric ammonium citrate.

Myeloma cells were cultured in vitro in media lacking transferrin and tropolone (lipophilic chelator) but in the presence of 0.2 mg/l of ferric ammonium citrate in suspension culture (see e.g. example 5, line 29-31). As depicted in figure 1, the control cultures do not contain chelators. The disclosure of Fields et al states that the cells do not survive after 48 hours. Nonetheless, the cells are cultured in media meeting the requirements of the instant claims. Furthermore, as the media requirements overlap that of the instant claims, one would expect those of Fields et al to be as successful as that of the instant claims. As evidenced by the instant

specification, the concentration of 1.25 mg/L of ferric ammonium citrate is about 0.2 mg/L of iron. Hence, the iron concentration is about 0.03 mg/L. The media was serum-free see example 2.

In the absence of either tropolone or transferrin but in the presence of 0.2 mg/l ferric ammonium citrate myeloma cells failed to thrive and died within 48 hours.

Myeloma cells were cultured in vitro in suspension culture in media lacking transferrin, lipophilic chelators and nitrogen containing chelators but in the presence of ferric chloride-sodium citrate (see e.g. ¶ 0094). Iron is in the concentration of **0.28 mg/L to 11 mg/L** (see e.g. ¶ 0113). As evidenced by the instant specification, the concentration of 1.25 mg/L of ferric ammonium citrate is about 0.2 mg/L of iron.

> [0153] In a preferred embodiment, the replacement medium of the present invention is used to grow CHO cells in suspension culture. In another preferred embodiment, the replacement medium of the present invention is used to grow hybridoma cells in suspension culture. In yet another preferred embodiment, the replacement medium of the present invention can be used to culture NS/O myeloma cells in suspension culture. If NS/O myeloma cells are cultured, the replacement 1.times. medium of the present invention can be supplemented with a lipid mixture supplement (see Table 3).

The replacement media also most explicitly contains iron in place of transferrin.

> [0112] In the replacement media of the invention, any basal media may be used. Such basal media may contain one or more amino acids, one or more vitamins, one or more inorganic salts, one or more buffer salts, and one or more lipids. In accordance with the invention, **transferrin is replaced with iron or an iron-containing compound a**nd/or insulin is replaced with zinc or a zinc containing compound. Preferably, iron chelate compounds are used in accordance with the invention
>
> [0113] Fe.sup.2+ and/or Fe.sup.3+ chelate compounds which may be used include but are not limited to compounds containing an Fe.sup.2+ and/or Fe.sup.3+ salt and a chelator such

as ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis(.beta.-aminoethyl ether)-N,N,N,N'-tetraacetic acid (EGTA), deferoxamine mesylate, dimercaptopropanol, diethylenetriaminepentaacetic acid (DPTA), and trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CDTA). For example, the iron chelate compound may be a ferric citrate chelate or a ferrous sulfate chelate. Preferably, the iron chelate compound used is ferrous sulphate.7H.sub.2O EDTA (FeSO.sub.4O.7H.sub.2O EDTA, e.g., Sigma F0518, Sigma, St. Louis, Mo.). In the medium of the present invention, the concentration of Fe.sup.2' and/or Fe.sup.3+ can be optimized using only routine experimentation. **Typically, the concentration of Fe.sup.2+ and/or Fe.sup.3+ in the 1.times medium of the present invention can be about 0.00028 to 0.011 g/L.** Preferably, the concentration of iron is about 0.0011 g/L.

Gorfien teaches media for culturing myeloma wherein the iron concentration is between 0.28 and 11 mg/L Hence, the iron concentration would be about 1.75-68.75 mg/L of ferric ammonium citrate.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use ferric ammonium citrate as taught by Field et al in the media taught by Gorfien et al because Gorfien et al teach that it is within the ordinary skill of the art to use particular levels of iron to culture myeloma cells and because Gorfien et al teach that it is within the ordinary skill of the art to use ferric ammonium citrate as a source of iron. In KSR International Co. v. Teleflex lnc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that

obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, Gorfien and Field et al are both directed at methods of culturing myeloma cells. The combination of the two represents the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (Id. At 1395.) Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to applicants' arguments

Applicants have traversed the rejection under 35 USC 103 in the amendment filed 2/7/11. Applicants argue that Gorfien and Field et al do not explicitly demonstrate that growing myeloma cells in transferrin free media is possible. As support, applicants note that the art teaches that replacing transferrin at low concentrations (0.2 mg/L iron) does not support the growth of myeloma cells. Secondly, applicants argue that given the correspondence between growth ability of hybridoma and myeloma cells and the lack of explicit results, one can understand lack of growth in hybridoma cells to be relevant teachings extrapolated to myeloma cells.

These arguments have been considered but are not persuasive for the following reasons. Dealing with the later argument, if hybridoma cells represent the state of the art with myeloma cells than Fields et al teaches that in concentrations embracing those of the instant claims,

hybridoma cells survive with Fe2+ up to about 8 mg/L, however, growth is improved between 0.1 and1.5 mg/L. Hence, one would expect the same results to occur for myeloma cells.

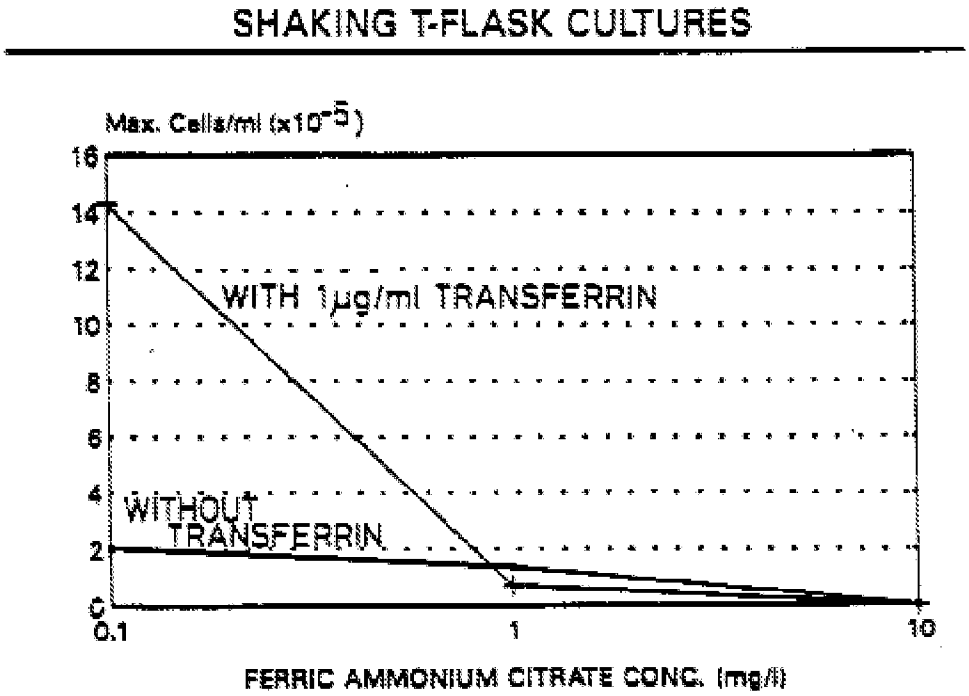

FIG. 2B

As well, Field et al teach that in vitro cultured myeloma cells are viable for up to 48 hours, during which one would expect the cells to have doubled.

Gorfien improves upon these methods by increasing the concentration of iron. Gorfien et al propose cellular culture methods with a concentration of iron that is 0.28 mg/L-11/mg/L, a concentration that is higher than the art had previously established. Applicants argue that the ability of the improved culture media to mediate or ameliorate myeloma growth conditions in the absence of transferrin or other lipophilic or nitrogen containing chelators is not explicitly shown

in Gorfien et al. In response it is noted that it has established that an applicant's invention is not limited to the exemplified methods but to that which is disclosed and Gorfien et al is directed to development of mammalian cell culture media

> [abstract] The present invention provides a cell culture medium formulation that supports the in vitro cultivation, particularly in suspension, of mammalian cells, particularly epithelial cells and fibroblast cells, and methods for cultivating mammalian cells in suspension in vitro using these media. The media comprise a basal medium and a polyanionic or polyanionic compound, preferably a polysulfonated or polysulfated compound, and more preferably dextran sulfate. The present invention also provides chemically defined, protein-free eukaryotic cell culture media comprising an iron chelate and zinc, which is capable of supporting the growth (and particularly the high-density growth of mammalian cells) in suspension culture, increasing the level of expression of recombinant protein in cultured cells, and/or increasing virus production in cultured cells.

Wherein this media is to be used for suspension cells including 293, CHO, hybridoma cells and myeloma cells.

> [0158] 293 human embryonic kidney cells and HeLaS3 cells are particularly preferred for growth in the suspension medium of the present invention. Chinese hamster ovary (CHO) cells, NS/O cells, and hybridoma cells are particularly preferred for growth in the replacement medium of the present invention. Especially preferred are CHO cells.

Gorfien is directed towards overcoming limitations in the art related to media formulations such as 1) the lack of standardization of sera between lots 2) improved cell growth in serum-free media 3) immunogenic properties of some animal peptide supplements used for serum-free media. The goal is to prepare a media that is chemically defined, protein free and facilitates the growth of mammalian cells to high density and/or increases the level of expression of recombinant proteins, reduces cell clumping and does not require supplementation with animal proteins such as transferrin and insulin. To this end, Gorfien et al recognizes that use of iron chelate is important.

[0053] The medium of the present invention is a chemically defined formulation which contains no protein or hydrolysates of either plant or animal origin. Although the invention is not bound by any particular theory, it is believed that the ability of the medium of the present invention to facilitate the growth of mammalian cells **is due to the replacement of insulin by zinc and/or the replacement of transferrin with an iron chelate**. Moreover, when supplemented with dextran sulfate, the medium facilitates growth (in particular, the high-density growth of any of mentioned mammalian cells, and particularly those described above, and preferably, CHO cells, PER-C6 cells, and 293 cells) in suspension culture, increases the level of expression of recombinant protein in cultured cells, and/or increases virus production in cultured cells without clumping.

To the extent that ferric and ferrous is included in the formulations, the exact particulars of the replacement compound do not appear to be the invention.

> [0113] Fe.sup.2+ and/or Fe.sup.3+ chelate compounds which may be used include but are not limited to compounds containing an Fe.sup.2+ and/or Fe.sup.3+ salt and a chelator such as ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis(.beta.-aminoethyl ether)-N,N,N,N'-tetraacetic acid (EGTA), deferoxamine mesylate, dimercaptopropanol, diethylenetriaminepentaacetic acid (DPTA), and trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CDTA). For example, the iron chelate compound may be a ferric citrate chelate or a ferrous sulfate chelate. Preferably, the iron chelate compound used is ferrous sulphate.7H.sub.2O EDTA (FeSO.sub.4O.7H.sub.2O EDTA, e.g., Sigma F0518, Sigma, St. Louis, Mo.). In the medium of the present invention, the concentration of Fe.sup.2' and/or Fe.sup.3+ can be optimized using only routine experimentation. Typically, the concentration of Fe.sup.2+ and/or Fe.sup.3+ in the 1.times. medium of the present invention can be about 0.00028 to 0.011 g/L. Preferably, the concentration of iron is about 0.0011 g/L.

A review of the art demonstrates that iron replacements comprise a number of formulations that are used interchangeably and these include the indication that ferric ammonium citrate is a ferric citrate chelator. In other words, ferric ammonium chelate appears to be a ferric citrate chelate by name absent evidence to the contrary. Hence, Fields et al provides description of those items encompassed by but not explicitly disclosed by Gorfien et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD

Primary Examiner
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